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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,191	02/27/2007	Shuibing Chen	014740-001020US	4061

20350 7590 03/13/2009

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	
MAIL DATE	**DELIVERY MODE**
03/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,191	CHEN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8-21-07, 12-18-08* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-8-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Formula 1 (paragraph 0048) from the genus 2,6 disubstituted purine in the reply filed on 12-18-08 is acknowledged. The traversal is on the ground(s) that claim 20 is directed to a method of identifying compounds that induce dedifferentiation and any test compound can be used with this method. Multiple compounds can be tested and the compound's activity for the state purpose can be determined. This is not found persuasive because there are numerous possibilities for the substituents of a 2,6-disubstituted purine and even the elected Formula 1 species still encompass several different test compounds for the instant invention. The substituents of a 2,6-disubstituted purine can result in compounds that lack the same core structure or special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 20-27 with the nonelected species including substituted purines other than disubstituted purines, pyrimidines, quinazolines, pyrazines, pyrrolopyrimidine, pyrazolopyrimidine, phthalazines, pyridazines, and quinoxalines, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12-18-08.

Applicants' amendment filed 8-21-07 and 12-18-08 have been entered. Claims 1-19 and 28-34 have been canceled. Claims 20-27 and the Formula 1 species from 2,6-disubstituted purines are under consideration.

Drawings

3. The drawings (replacement sheets) were received on 8-21-07 and 12-18-08. These drawings are accepted.

Information Disclosure Statement

4. The references FR 2793794, WO 02/051843 and WO 00/71543 in the information disclosure statement filed 6-8-07 fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because No translation of those references have been provided. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification

5. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to **a single paragraph on a separate sheet within the range of 50 to 150 words**. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract on the cover page on WO 2005/047524 A2 only has 13 words. The abstract should be in narrative form and generally limited to **a single paragraph on a separate sheet within the range of 50 to 150 words**. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "ob" in claim 27 is vague and renders the claim indefinite. The term "ob" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term "ob" would be remedial.

The term "Ucp" in claim 27 is vague and renders the claim indefinite. The term "Ucp" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term "Ucp" would be remedial.

The term "PPARγ" in claim 27 is vague and renders the claim indefinite. The term "PPARγ" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term "PPARγ" would be remedial.

The term "C/EBPs" in claim 27 is vague and renders the claim indefinite. The term "C/EBPs" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term "C/EBPs" would be remedial.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 20-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at

the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 20-27 are directed to a method of identifying compounds that induce dedifferentiation of linage committed mammalian cells into multipotent stem cells comprising contacting a mammalian cell with a test compound, which is elected Formula 1 species from 2,6-disubstituted purines, culturing said cells in a first cell culture media that induces differentiation of the multipotent stem cell into a first cell type, and culturing said cells in a second cell culture media that induces differentiation of the multipotent stem cell into a second cell type, wherein induction of differentiation into both first and second cell types identifies the test compound as a dedifferentiation compound. Claim 21 specifies the first cell culture medium induces osteogenesis and the second culture medium induces adipogenesis, wherein the first cell type is an osteoblast and the second cell type is an adipocyte. Claims 24 and 25 specify induction of osteogenesis is detected by expression of an osteogenesis marker gene and induction of adipogenesis is detected by expression of an adipogenesis marker gene, respectively. Claims 26 and 27 specify the marker gene for osteogenesis and adipogenesis, respectively.

The specification discloses that murine C2C12 cell is a myogenic lineage committed myoblast, exposure of C2C12 cells to a 2-(4-morpholinoanilino-6-cyclohexylamino-purine analog (compound A or reversine, Figure 2) induces high level (7 fold) of alkaline phosphatase (ALP) activity relative to the DMSO control treatment. Reversine inhibits myotube formation and myogenic specific marker such as MyoD and myosin begin to disappear. After 4 days of treatment with reversin, the compound was removed and cells were grown in osteogenic differentiation medium (ODM) or adipogenic differentiation medium (ADM), and 35% of cells

stained positive for ALP and 40% of cells had the characteristic fat cell morphology and stained positive for Oil Red O, respectively (e.g. Examples 3 and 4). The claims encompass inducing dedifferentiation of any lineage committed mammalian cell to multipotent stem cell, identification of the multiple stem cell, differentiation of said multipotent stem cell into various cell types and identification of said cell types. The mammalian cell can be any cell type, such as epithelial cell, endothelial cell, fibroblast, skeletal muscle cell, smooth muscle cell, glial cell, and neuronal cell etc., and the cell can be derived from numerous different mammals, such as mice, rats, other rodents, humans, monkey, baboons, chimpanzee, other primates, horse, cows, pigs, sheep, dogs, cats, whales, and other mammals etc. The specification fails to provide adequate guidance and evidence for how to identity multipotent stem cells of different cell types derived from numerous different mammals, and how to identify numerous different cell types differentiated from said multipotent stem cells derived from various mammals.

The cell markers for multipotent stem cells and for differentiated mammalian cells differ among different cell types and different mammalian species. There are dramatic molecular and cellular differences between human and mouse embryonic stem cells. Allegrucci et al., 2006 (Human Reproduction Update, Vol. Advance Access published on August 26, 2006, p. 1-18) demonstrates that there is difference in pluripotency marker molecules, transcriptional profiling, genetic stability and epigenetic stability even among different human embryonic stem cell lines (e.g. abstract). There are differential expression of different markers among different human ES cell lines and "[t]he physiological significance of expression of these markers is not clear, and it is likely that the limited panel of markers in current use may be insufficient to define the state of 'stemness' because many of them are not unique to embryonic stem cells" (e.g. p. 2, right

column). Sato et al., 2003 (Developmental Biology, Vol. 260, p. 404-413) shows that there are 918 different gene expressions between human embryonic stem cell line H1 (HESC H1 line) and mouse embryonic stem cells (MESCs) (e.g. Figure 4A). There are molecular markers that are unique for HESCs as compared to MESCs, for example, SOCS-1, an inhibitor of the STAT-3 signaling pathway, is enriched in HESCs but not in MESCs (e.g. p. 412, left column, 3rd paragraph). Sato also suggests that different human ES lines have different transcriptional profiles and respond differently to the differentiation conditions (e.g. p. 412, left column, last paragraph). Rao, M., 2004 (Developmental Biology, Vol. 275, p. 269-286) reports some known differences between mice and human ES cells (e.g. table 3). The difference between mice and human ES cells is much higher than that seen in human-to-human cell comparison (e.g. p. 282, left column, 1st paragraph). Indeed, there are different molecular markers even among different human ES cells. Abeyta et al., 2004 (Human Molecular Genetics, Vol. 13, No. 6, p. 601-608) compares gene expression profiles of different human ES cell lines, HSF-1, HSF-6 and H9 lines. Abeyta observed that each line has a unique expression signature and the expression of many genes was limited to just one or two hESC lines. Abeyta suggests that "the observed differences in gene expression between independently-derived hESC lines may reflect inherent differences in the initial culture of each line and/or the underlying genetics of the embryos from which the lines were derived" (e.g. abstract). It appears that human, rat and mouse ES cells could have different specific cell markers (human and mice have dramatically different expression profiles) and the cell markers could be different even among different human ES cells, and there are differential expression even among common cell markers. Differences in gene expression between independently-derived hESC lines may reflect inherent differences in the initial culture

of each line and/or the underlying genetics of the embryos from which the lines were derived, and they can respond differently to the differentiation conditions.

Similarly, the expression profiles among human, rat and mice hair follicle stem cells could differ dramatically. Yu et al., 2006 (American Journal of Pathology, Vol. 168, No. 6, p. 1-6) points out that human hair follicle-derived stem cells are not able to proliferate using the medium condition as disclosed by the prior art and suggests different biological behaviour of mouse and human stem cells and further points out that "[n]estin is a marker for neural progenitor cells" (e.g. p. 8, left column). Cotsarelis, G., 2006 (The Journal of Clinical Investigation, Vol. 116, No. 1, p. 19-22) reports that there are differences between mouse and human hair follicle stem cell markers, "[I]n particular, CD34, which delineates hair follicle stem cells in mouse, is not expressed by human hair follicle stem cells, while CD200 is expressed by stem cells in both species" (e.g. abstract). There are other genes that are expressed in human hair follicle stem cells but not expressed in mouse hair follicle stem cells, including PHLDA1, FOLLISTATIN and DI02 (e.g. Table 1). Cotsarelis further points out that "the cellular and molecular characteristics of stem cells in the human follicle could be quite different from those in the rodent" (e.g. p. 20, right column). It appears that human, rat and mouse hair follicle stem cells could have different specific cell markers and it is unclear what would be the cell marker for the human and rat hair follicle stem cells. It was unpredictable what would be the cell markers for various different human, rat and mouse hair follicle stem cells. It was known in the art that a stem cell expresses various different specific cell markers, which specifically defines said stem cells. It is apparent that cell markers to identify multipotent stem cells or differentiated mammalian cells vary among different multipotent stem cells, different cell types and different

mammalian species, and even vary among different cell lines. The specification only discloses cell markers for the identification of osteoblasts and adipocytes but fails to provide adequate guidance for how to identify the vast number of multipotent stem cells, various cell types, and cells derived from tens of thousands of different mammalian species. Absent specific guidance, one skilled in the art at the time of the invention would not know how to identify compounds that induce dedifferentiation of various lineage committed mammalian cells into numerous different multipotent stem cells.

The claims encompass using numerous different test compounds but the specification fails to provide adequate guidance and evidence for what kind of multipotent stem cells can be induced by those various test compounds. The test compounds have diverse functions and effects on different mammalian cell types and it is unclear what kind of multipotent stem cells can be induced from various mammalian cells derived from numerous different mammalian speices. The specification also fails to provide specific guidance for the differentiation media required for various multipotent stem cells to differentiate into various cell types. There is also a lack of correlation between the lineage committed mammalian cells and the differentiated first and second cell type so as to determine that the test compound is indeed a compound that induce dedifferentiation of lineage committed mammalian cells. The differentiated first and second cell types must be lineage correlated to the lineage committed mammalian cells exposed to the test compound such that differentiation of a multipotent stem cell into both first and second cell types could be used as an indicator that said test compound is a compound that induces dedifferentiation of lineage committed mammalian cells. Absent specific guidance, one skilled in the art at the time of the invention would not know how to practice the claimed invention.

Further, the claims read on contacting a mammalian cell with a test compound, culturing said cells to induce differentiation of multipotent stem cell into a first and a second cell type, and induction of differentiation into both first and second cell type would identify the test compound as dedifferentiation compound. It appears that the test compound is the compound that induces differentiation of multipotent stem cell into a first and a second cell type, therefore, the test compound should be a "differentiation" compound rather than a "dedifferentiation" compound. It is unclear how a test compound that induce differentiation of multipotent stem cell into differentiated mammalian cell can be considered a compound that induce dedifferentiation of lineage committed mammalian cells into multipotent stem cells. Thus, the claims are not enabled to identify compounds that induce dedifferentiation of lineage committed mammalian cells into multipotent stem cells as claimed.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of one of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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